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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,451	12/21/2000	Saverio Carl Falco	BB-1179	1431

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,451	FALCO ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *alignment* .

DETAILED ACTION

Status of the Application

Claims 13-25 are pending.

Applicant's cancellation of claims 1-12, addition of claims 13-25 and election without traverse of Group III, drawn to the nucleic acid of SEQ ID NO: 5 and polynucleotides encoding the polypeptide of SEQ ID NO: 6, a host cell and a method of use, in Paper No. 7, filed on 1/6/2003 is acknowledged.

It is noted that claims 1-12 were inadvertently restricted under 35 USC 121 instead of under 35 USC 121 and 372 (Lack of Unity) in view of the fact that the instant application was filed under 35 USC 371. However, the claims would have been restricted in exactly the same Groups as those indicated in the previous Office Action Paper No. 5, mailed on 7/16/2003 for the reasons already set forth in Paper No. 5. Furthermore, since Applicants have cancelled claims 1-12 and new claims 13-25 are drawn to the polynucleotide of SEQ ID NO: 5 or polynucleotides encoding the polypeptide of SEQ ID NO: 6, the issue of whether the claims should have been restricted under 35 USC 121 and 372 is no longer relevant. As such, the Examiner will proceed with the examination of the pending claims as follows.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/092869 filed on 7/15/1998.

2. This application is the national stage application of PCT/US99/15916 filed on 7/14/1999, in accordance with 35 U.S.C. 371.

3. It is noted that the polynucleotide of SEQ ID NO: 5 was first disclosed in provisional application No. 60/092869 filed on 7/15/1998, and the polypeptide of SEQ ID NO: 6 (408 amino acids) was first disclosed in PCT/US99/15916 filed on 7/14/1999.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 4/16/2001 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 13-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 13 (claims 14-25 dependent thereon) is indefinite in the recitation of "nucleic acid fragment that is complementary to (a)" for the following reasons. The subject matter in (a) refers to a nucleotide sequence whereas the subject matter of (b) is a nucleic acid fragment. It is suggested that the claim be amended to recite "nucleic acid...wherein the nucleotide sequence of said nucleic acid.....is complementary to (a)" or similar. It is noted that if the intended nucleic acid in (b) is one having the entire complementary sequence of that recited in (a), the term "complementary" should recite "completely complementary". For examination purposes, the

subject matter in (b) will be interpreted as "any polynucleotide comprising a fragment of the complete complement of a polynucleotide which has the sequence as described in (a)". Correction is required.

8. Claim 7 is indefinite in the recitation of "sequence comprises one of SEQ ID NO: 5" as it is unclear which additional sequences being referred to in addition to SEQ ID NO: 5. It is suggested that if the intended sequence is SEQ ID NO: 5 only, the term "one of" be deleted. For examination purposes, the term "one of" will not be given patentable weight. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-19 are directed to a genus of polynucleotides of any function comprising a fragment of the complete complement of polynucleotides encoding a 5,10-methylenetetrahydrofolate reductases wherein said reductases have 85%, 90%, 95%, 100% sequence identity to the polypeptide of SEQ ID NO: 6. Claims 20, 21 and 25 are drawn to a method of transforming a cell with the genus of polynucleotides as described above, a cell

transformed with said genus of polynucleotides or to a method of use of such transformed cell. Claims 22, 23 and 24 are drawn to a method of transforming a plant with said genus of polynucleotides or to a plant/seed comprising said genus of polynucleotides. While the specification provides the structure and function of the polypeptide of SEQ ID NO: 6, there is no disclosure of the function of polynucleotides comprising fragments of polynucleotides encoding the polypeptide of SEQ ID NO: 6 nor there is disclosure of the function of polynucleotides comprising fragments of polynucleotides encoding homologs of the polypeptide of SEQ ID NO: 6 as encompassed by the claims. In addition, there is no disclosure of which fragments in a polynucleotide encoding the polypeptide of SEQ ID NO: 6 are associated with 5,10-methylenetetrahydrofolate reductase activity.

While one could argue that the claimed genus of polynucleotides is adequately described since one can isolate polynucleotides encoding proteins of similar function by sequence comparison using the polypeptide structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun

et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a single species of the genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO: 5 or polynucleotides encoding the polypeptide of SEQ ID NO: 6, does not reasonably provide enablement for polynucleotides comprising a fragment of the complete complement of polynucleotides encoding the 5,10-methylenetetrahydrofolate reductase of SEQ ID NO: 6 or homologs thereof as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in regard to the large number of polynucleotides of unknown function encompassed by the claims. While the structure and function of the polypeptide of SEQ ID NO: 6 (and its corresponding polynucleotide) have been disclosed, there is no disclosure of the function of polynucleotides comprising fragments of the polynucleotide of SEQ ID NO: 5 or the polynucleotides which encode the polypeptide of SEQ ID NO: 6. Furthermore, no disclosure of which fragments in the polynucleotide of SEQ ID NO: 5 or a polynucleotide encoding the polypeptide of SEQ ID NO: 6 are indicative of 5,10-methylenetetrahydrofolate reductase activity has been made. As indicated above, the state of the art clearly teaches the unpredictability of the art in regard to assigning function based on sequence homology. See the teachings of Bork (Genome Research, 10:398-400, 2000), Broun et al. (Science 282:1315-1317, 1998), Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed. Since the amino acid sequence of a protein determines its function, one of skill in the art would require some knowledge or guidance as to how structure correlates with function to isolate polynucleotides encoding proteins of similar function. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on sequence homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) screen and isolate those polynucleotides, as encompassed by the claim, which encode proteins of similar function to that disclosed for the polypeptide of SEQ ID NO: 6, or (2) determine the actual function of the claimed polynucleotides. Thus, Applicant has

not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 13-16, 18-21, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Rozen et al. (WO-9533054, 1995; cited in the IDS). Rozen et al. teaches a polynucleotide which encodes a human methylene-tetrahydrofolate reductase, as well as its corresponding complete complement. The reductase of Rozen et al. comprises several fragments of the polypeptide of SEQ ID NO: 6, therefore the polynucleotide of Rozen et al. comprises a fragment of a polynucleotide encoding the polypeptide of SEQ ID NO: 6. See attached alignment. Claims 13-16 are directed to a polynucleotide which comprises a fragment of the complete complement of a polynucleotide encoding the polypeptide of SEQ ID NO: 6. Since the complete complement of the polynucleotide of Rozen et al. is a polynucleotide which comprises a fragment of the complete complement of a polynucleotide of SEQ ID NO: 6, the claims are anticipated as written.

Claims 18-21 are drawn to vectors and host cells comprising the polynucleotide already described or to a method of producing a methylenetetrahydrofolate reductase with the vector. Rozen et al. also teaches the construction of vectors comprising the polynucleotide linked to a promoter induced by IPTG, transformation of E. coli cells with said vector and production of the corresponding reductase by cultivation of the host cell under conditions which would allow expression of the polynucleotide (page 33, line 31-page 35, line 9). Therefore, the teachings of Rozen et al. also anticipate claims 18-21 as written.

Conclusion

13. No claim is in condition for allowance.

14. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

15. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
February 28, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1600